Remarks/Arguments

A. Summary of the Claims

Claims 1-12 are pending and are presented for reconsideration.

B. The Written Description Rejection Is Overcome

1. Summary of Rejection and the Written Description Standard

Claims 1-12 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Specifically, the Examiner contends that the phrase "distinct mean particle sizes" is not supported in Applicants' specification.

Applicants disagree. The pending claims satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. The issue of written description is "determined on a case-by-case basis and is a question of fact." MPEP § 2163.04. An examiner "has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." *Id.*

It is well-settled that the written description requirement is satisfied if a specification describes "the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." MPEP § 2163[I]. In fact, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice...." *Id.* at § 2163.02.

Additionally, "[t]he subject matter of the claim need not be described literally (*i.e.*, using the same terms or in haec verba) in order for the disclosure to satisfy the description requirement." *Id.* Rather, an added claim limitation can "be supported in the specification through express, implicit, or inherent disclosure." *Id.* at § 2163[I][B] (emphasis added); *see also* § 2163[II][A][3](a) (noting that "[i]f a skilled artisan would have understood the inventor to be

in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met").

With this in mind, Applicants will now address the written description rejection and explain how the specification satisfies 35 U.S.C. § 112, first paragraph.

2. The Phrase "distinct mean particle size" Is Supported In Applicants' Specification

Contrary to the Examiner's position, the specification provides a written description for the phrase "distinct mean particle size." For example, referring to paragraph [0003], the active ingredients of Diclectin, namely Doxylamine Succinate and Pyridoxine HCl, are commercially "in the form of powders having different granular sizes which makes it very difficult to uniformly mix them in a dry state along with required excipients" and that "this poses a content uniformity challenge during manufacturing of final dosage forms" are described. (Emphasis added).

Referring, for example, to paragraph [0004] it is further explained that another aspect of the content uniformity challenge is due to the "small size" of the pyridoxine HCl (about 60 microns) particles and their tendency to easily adhere to manufacturing vessels for example, which causes ingredient losses.

Paragraph [0014] of the specification further specifies that against expectations, the use of a roller compactor alleviates ingredient losses during manufacturing and allows for vast improvement of the content uniformity in terms of active ingredients. Indeed, roller compaction standardizes the particle size of the active ingredients (which would otherwise not be uniform, as stated in paragraph [0003]), thereby avoiding poor mixing of active ingredients or losses due to fines which adhere to processing equipment or which do not flow properly.

Furthermore, paragraph [0020] emphasizes the fact that roller compaction results in granules of essentially uniform size distribution, which addresses the "problem of size difference of the initial powdered ingredients." (Emphasis added). As an example, it is noted that "the ingredient Pyridoxine HCl and Doxylamine Succinate are no longer of different mean particle diameter [...]".

Thus Applicants respectfully submit that it is clear from the specification as filed that Applicants were in possession of a method including "distinct mean particle sizes," as recited in the instant claims. Applicants further respectfully submit that it is clear from the specification that it is not roller compaction that leads to distinct mean particle sizes. To the contrary, as demonstrated in the specification and explained above, roller compaction results in granules of essentially uniform size distribution, which addresses the "problem of size difference of the initial powdered ingredients". (Emphasis added).

In view of the evidence submitted by the Applicants, it is clear that the specification provides a written description for the phrase "distinct mean particle sizes." Therefore, the rejection of claims 1-12 under 35 U.S.C. § 112, first paragraph, is improper and should be withdrawn.

C. The Obviousness Rejection Is Overcome

1. Summary of the Rejection and Summary of Applicants' Arguments

Claims 1-12 are rejected under 35 U.S.C. § 103(a) as being obvious over Chen (U.S. Pat. No. 5,260,069) in view of Chu *et al.* (U.S. Pat. No. 6,419,954) and Bishai *et al.* In summary, the Examiner contends that the primary reference, Chen, "...discloses a process for preparation of pulsatile particles which can contain combinations of therapeutic agents in which the granule containing the active agents and swelling agent are prepared by the well known and economic roller compaction method." Office Action at page 2-3. As for Chu *et al.*, it is relied upon for

apparently disclosing "....embodiments in which a tablet can further include untreated active agents (*e.g.*, without coating material or powders) in addition to the active agent containing particles and that the active agent particles can contain vitamins or drugs...." *Id.* Bishai *et al.* is cited as disclosing "...the combination of 10 mg doxylamine succinate and 10 mg pyridoxine HCl is safe and effective in treating nausea and vomiting associated with pregnancy." *Id* at page 3.

The Examiner concedes that the cited art fails to "disclose the use of more than one active ingredient, such as the combination of doxylamine succinate and pyridoxine HCl." *Id.* In an effort to supplement the deficiencies of the prior art, the Examiner contends that a person of ordinary skill in the art "...would have been motivated to modify the prior art as above with the expectation that the combination of doxylamine succinate and pyridoxine in granules prepared by roller compaction and sieving to obtain appropriate mesh size would be safe and effective in treating NVP." *Id.*

Applicants disagree. Applicants respectfully reiterate that the ordinary person of skill in the art would clearly understand the meaning of "distinct mean particle sizes" from the specification as filed, and that the instant claims are not rendered obvious by the cited references. As explained in the following section, the cited art references fail to disclose at least this aspect of the present invention. This alone overcomes the obviousness rejection. MPEP § 2143.03 ("To establish a prima facie case of obviousness... the prior art reference (or references when combined) must teach or suggest all the claim limitations."). Further, there is no motivation to modify or combine the references, and there is no reasonable expectation of success that such modifications or combinations would work. *Id.*

2. The Prior Art Fails to Disclose "multiple powdered active ingredients comprising distinct mean particle sizes"

Applicants reiterate that both Chen and Chu *et al.* focus on the technical problems of obtaining either a "pulsatile" (Chen at Abstract) or a "modified" (Chu *et al.* at Title and Abstract) release of the active ingredient, and thus on the composition of the membrane, coating or gel-forming matrix that surround the pellets or particles before compression. Such technical problems are different from that of the present invention, namely to alleviate ingredient loss during the manufacturing of heterogeneous powderous multi-ingredient medicaments and to provide superior content uniformity results (Applicant's specification at page 2, [0006]). Further, these references do not appear to disclose "pharmaceutical dosage forms comprising multiple powdered active ingredients comprising distinct mean particle sizes"—much less a method for preparing such dosage forms.

As for Bishai *et al.*, it appears to disclose that the combination of both doxylamine succinate and pyridoxine hydrochloride (as found in DiclectinTM) is safe and effective in the treatment of nausea and vomiting during pregnancy. Bishai *et al.* at pages 167, 170, 173-177. Bishai *et al.* fail to disclose or suggest any aspect of a method for preparing a formulation including these active ingredients—much less Applicant's claimed method of preparing "pharmaceutical dosage forms comprising multiple powdered active ingredients comprising distinct mean particle sizes."

Thus, all of the cited references fail to disclose or even suggests the technical problem of having "multiple powdered active ingredients comprising distinct mean particle sizes" involved in a process of preparation of a pharmaceutical dosage form. Therefore, the present obviousness rejection is overcome and should be withdrawn. MPEP § 2143.03.

3. There Is No Motivation to Modify the Cited References

A person of ordinary skill in the art would not find, in any of the cited references, or in the knowledge generally available to him or her, any suggestion or motivation to modify Chen or to combine its teachings with Chu *et al.* and Bishai *et al.* to obtain Applicant's claimed invention.

For instance, Chu *et al.* explains that "any suitable granulation methods can be used to produce particles comprising an active agent." Chu *et al.* at col. 12, lines 25-26. Either wet or dry granulation methods can be used. *Id.* at col. 12, lines 29-31. These statements confirm that several possible techniques are contemplated. Stated another way, there is no motivation to use Applicant's claimed "method for the preparation of pharmaceutical dosage forms comprising multiple powdered active ingredients comprising distinct mean particle sizes." See MPEP § 2143.01 ("The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination."). Further, Applicant respectfully notes that "obvious to try" is not the appropriate standard under 35 U.S.C. § 103. The Gillette Co. v. S.C. Johnson & Son, Inc., 919 F.2d 720 (Fed. Cir. 1990) (noting that "'obvious to try' is not to be equated with obviousness under 35 U.S.C. 103.").

In addition, as acknowledged by the Examiner, Chen and Chu *et al.* both fail to disclose or suggest the use of more than one active ingredient in the preparation of granules, particles, or pharmaceutical dosage forms. Further, as explained above, there is no disclosure in the cited references to use "multiple powdered active ingredients comprising distinct mean particle sizes" in the preparation of a pharmaceutical dosage form. This is evidence that there is no reasonable expectation of success that modifying or combing the cited references to obtain Applicant's claimed invention would work.

In view of the above, it is clear that a person of skill in the art would not have been motivated to modify Chen or to combine its teachings with Chu *et al.* and Bishai *et al.* to obtain Applicant's claimed invention. Further, there is no reasonable expectation of success that such a combination or modification would work. Therefore, at least two additional elements necessary to establish a *prima facie* case of obviousness are missing.

Because all three elements necessary to establish a *prima facie* case of obviousness are missing, the present obviousness rejection is overcome. Therefore, Applicant requests that this rejection be withdrawn.

4. Additional Considerations

Applicant also notes that the roller compacting method provided surprising and unexpected results as to alleviation of ingredient losses during manufacturing of heterogeneous powdered active ingredients and as to content uniformity in terms of active ingredients (see, *e.g.*, Applicant's specification at page 5, [0014]).

The examples in the instant application are conducted using Pyridoxine HCl and Doxylamine Succinate as active ingredients, which are said to have distinct mean particle diameters (*see id.* at page 1-2, [0004]). Applicant respectfully submits that a person of ordinary skill in the art would understand that the tested formulation in Examples 1 and 2 of the specification involved powdered active ingredients having distinct mean particle sizes.

This is further evidence of non-obviousness. *See In re Pravin*, 54 F.3d 746, 750 (Fed. Cir. 1995) ("One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of 'unexpected results,' *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.").

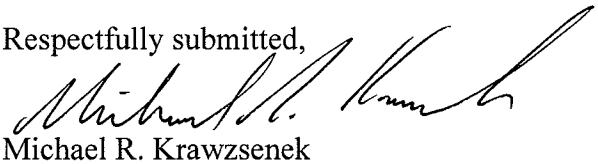
D. Conclusion

Applicants believe that the present document is a full and complete response to the Office Action mailed December 15, 2006. The present claims are in a condition for allowance, and such favorable action is requested.

It is believed that no fee is due for filing this document. However, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to this document, consider this paragraph such a request and authorization to withdraw the appropriate fee from Fulbright & Jaworski Deposit Account No. 50-1212/GOUD:037US.

The Examiner is invited to contact the undersigned Attorney at (512) 536-3020 with any questions, comments, or suggestions relating to the referenced patent application.

Respectfully submitted,



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